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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,150	09/10/2001	Kenneth J. Livak	9584-018	9176
20582	7590	05/03/2004	EXAMINER	
JONES DAY 51 Louisiana Aveue, N.W WASHINGTON, DC 20001-2113			FREDMAN, JEFFREY NORMAN	
			ART UNIT	PAPER NUMBER
			1637	

DATE MAILED: 05/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

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<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/816,150	LIVAK ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 14 August 2003.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-5,8-11 and 14-16 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-5,8-11 and 14-16 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

### Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 17, 2004 has been entered.

### ***Status***

2. Claims 1-5, 8-11, 14-16 are pending.

Claims 1-5, 8-11, 14-16 are rejected.

Any rejection which is not reiterated in this action is hereby withdrawn as no longer applicable.

### ***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-5, 8-11, 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hall et al (U.S. Patent 5,994,069) as applied to claims 1-5 and 8-10 in view of Wittwer et al (U.S. Patent

Hall teaches a method of detecting a target polynucleotide (see column 37) which comprises the steps of:

(a) contacting a target polynucleotide having a first portion and a second portion immediately contiguous to one another (see column 37, lines 34-36 and figure 25) with:

- (i) an invader oligonucleotide, at least a part of which is capable of specifically hybridizing to the first portion of the target polynucleotide (see column 37, lines 41-47 and figure 25);
- (ii) a probe oligonucleotide comprising a first region that is capable of specifically hybridizing to the second portion of the target polynucleotide and a flap region located adjacent to the first region (see column 37, lines 37-40 and figure 25);
- and (iii) a reagent that is capable of cleaving the flap region of the probe oligonucleotide when the probe oligonucleotide is hybridized to the second portion of the target polynucleotide and the invader oligonucleotide is hybridized to the first portion of the polynucleotide (see column 37, line 33 and figure 25);

under conditions such that the cleaved flap region of the probe oligonucleotide and the reagent can come into contact with a reporter precursor to which the flap region

of the probe oligonucleotide is capable of hybridizing to form a complex that can be cleaved by the reagent to provide a reporter capable of being detected (see column 37, figure 25);

(b) detecting the reporter to provide a signal (see column 8, lines 39-67 ); and

(c) determining whether the signal exhibits a specific behavior as a function of time (see figure 100, which shows a time course, here the time function is found in the basic control. That is, the control with no DNA target represents a time function of zero with regard to the completed reaction since the reaction cannot start while the actual value determined represents a time value of completed reaction. This relies upon a broad interpretation of the phrase "specific behavior as a function of time" in the claim and no definition limiting this phrase was found in the specification).

Hall further teaches the limitations of claims 2 and 3, where the invader oligonucleotide comprises, inherently (since any nucleic acid of more than two bases can have multiple regions) a first region and a second "flap" region which hybridizes to the target polynucleotide (see column 37, lines 30-40 and figure 25).

Hall further teaches the limitations of claims 4 and 5, where the invader oligonucleotide comprises, inherently (since any nucleic acid of more than two bases can have multiple regions) a first region and a second "flap" region which does not hybridize to the target polynucleotide (see column 38, lines 1-12 and figure 28, panel C).

Hall further teaches the limitations of claim 8-9 where the second portion is located immediately 3' to the first region (see figure 25) and where the "flap" of the invader is 3' to the region and the flap of the probe is 5' to the probe (see figure 25).

Hall teaches the limitation of claim 10 that the method is fluorescent signal detection (see column 8, lines 39-67, signal detection with fluorescent detection).

While Hall expressly recognizes background as a problem, noting "Background cleavage due to thermal breakdown of probe oligonucleotides can, when not resolved from specific cleavage products, reduce the accuracy of quantitation of target nucleic acids based on the amount of accumulated product in a set timeframe. (see column 54, lines 46-50), Hall does not teach modes of data analysis to overcome this issue of undesired background.

Wittwer, as per claims 1, 11 and 15, teaches solving the problem of background fluorescence by real time analysis of the signal as a function of time (see figure 2 and column 6) including on exonuclease type assays (see column 6, line 46). Wittwer expressly teaches, as relates to claims 6 and 7, non-linear behavior, which is quadratic, for the specific signal as shown by the curve in figure 5, where the linear fluorescence result is shown as negative and the curve is shown as positive. Wittwer provides the analytical framework for this analysis in column 7, especially lines 5-45. Wittwer discusses measuring the signal at a plurality of times to provide a data set as shown in figures 2 and 5, where sequential times or cycles are measured, fitting the

data to a polynomial function comprising a linear and quadratic term (as required by claims 15 and 16), here the derivatives (See column 7, line 57 to column 8, line 67), and determining whether the coefficient is greater than zero (column 8, lines 63-67). In particular, Wittwer is transforming the signal to a new domain, here the algorithm disclosed and comparing the shapes of the mathematical functions to determine whether the signal is positive or negative (see column 8 and figure 5, which shows a linear versus quadratic curve as negative versus positive for detection).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to solve the background problem of Hall using the methodology of Wittwer since Wittwer states that by use of his method the analytical "process is automated so that a user can prepare a biological sample and simply place it in a thermal cycler having a sensor for reporting fluorescence values as a function of cycle number and a processor programmed with an algorithm capable of processing the values and reporting a positive or negative result (see column 2, lines 53-58)". An ordinary practitioner would have been motivated to subject the method of Hall to the analytical method of Wittwer for the advantage of an automatic and rapid analysis of background which would distinguish positive from negative results. Further motivation is provided when Wittwer notes that the method may be applied to any amplification system (see column 5, line 47) including exonuclease probe designs such as those of Hall (see column 6, line 46). Lastly, motivation is provided by Hall's recognition that background is a problem and Wittwer's solution of the problem of background using

mathematical analyses of the shapes of the curves to distinguish the linear background from the exponential signal (see columns 7 and 8).

***Response to Arguments***

6. Applicant's arguments filed March 17, 2004, have been fully considered but they are not persuasive.

Applicant argues that the claimed invention does not require determination of the baseline region like Wittwer. This argument is not relevant since there is no element in the claims which distinguishes from the combination of Hall in view of Wittwer. Wittwer obtains a data set of time and signal as a function of time, Wittwer analyzes the data as a function of time by transforming the data set and Wittwer determines if the set exhibits non-linear behavior and then based upon the behavior of the data set, Wittwer detects or fails to detect the target molecule (see columns 7 and 8 of Wittwer, particularly the final section of column 8, lines 63-67 where Wittwer uses the analysis to detect whether the sample is positive or negative).

When Applicant argues the kinetics of figure 5 of Wittwer, that analysis is not performed with regard to the claim. The claim states "(b) obtaining a data set (t, S(t)), wherein t is time and S(t) is signal as a function of time, by detecting the reporter at a plurality of times; and (c) fitting (t, S(t)) to a quadratic function, transforming the quadratic function to yield a transformed function having independent and dependent variables having minima of zero and maxima of unity, and determining whether the transformed function exhibits non-linear behavior; wherein the target polynucleotide is detected if the transformed function exhibits non-linear behavior." As discussed in the



rejection, Wittwer teaches these steps. The entire issue and discussion regarding what Wittwer teaches fails to address itself to the claim. It is not relevant if Wittwer is performing "sliding window" analysis. Further, the emphasized point regarding negative results is not in the claim. So when Applicant argues that the analysis is used, in part, to determine a background window, this does not distinguish the claimed invention.

Applicant repeats the argument that there is no suggestion to combine the references. As stated previously, specific motivation is provided in the rejection. First the rejection notes that Wittwer solves the data analysis problem expressly recognized by Hall, which alone is express motivation to combine the teachings of Wittwer and Hall. However, the rejection continues to note that Wittwer expressly teaches that the analysis method is applicable to other amplification systems (see column 5, line 47) as well as other amplification methods such as exonuclease methods, which genus includes the Hall method (see column 6, line 46). Finally, the rejection concludes by identifying significant advantages in combining the method such as the ability to automate the method of Hall if the Wittwer analysis method is used. Consequently, there is significant motivation to combine these references.

### ***Conclusion***

7. This is an RCE of applicant's earlier Application No. 09/816,150. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL**


even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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